REMARKS

In response to the Final Office Action mailed August 3, 2006, Applicants respectfully request favorable reconsideration of the subject application in view of the following remarks.

Rejections Under 35 U.S.C. § 112

Claims 37, 40-41 and 44-46 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking an enabling disclosure. More particularly, the PTO asserts that no comparative levels of expression of SEQ ID NOs:7 and 75 in cancerous cells versus normal cells as being indicative of tumorigenesis is given in the specification. Further, the PTO asserts that, in order to be useful for the diagnosis of breast cancer, it would need to be shown that either the sequences of SEQ ID NOs:7 and 75 are expressed only in cancer tissue to the exclusion of normal tissue or are expressed at a significantly higher level in cancer tissue (overexpressed) as compared to normal tissues. The PTO alleges that Applicants have not shown evidence of this and thus that the claims are not enabled by the disclosure.

Applicants respectfully traverse the rejection on the following grounds.

Applicants submit that the specification as filed clearly describes that the recited sequences of SEQ ID NOs:7 and 75 are overexpressed in breast tumor tissue as compared to normal breast. For example, Example 5 starting on page 40 describes microarray analysis to identify polynucleotides that are at least two-fold overexpressed in breast tumor tissue samples as compared to normal breast tissue samples. At page 41, lines 18-23, the specification describes:

> Microarray analysis was performed on two microchips. A total of 3603 subtracted cDNA's and 197 differential display templates were evaluated to identify 40 candidates for further analysis by quantitative PCR. From these candidates, several were chosen on the basis of favorable tissue specificity profiles, including B305D, B311D, B726P, B511S and B533S, indicating their overexpression profiles in breast tumors and/or normal breast versus other normal tissues. It was evident that the expression of these genes showed a high degree of specificity for breast tumors and/or breast tissue. In addition, these genes have in many cases complementary expression profiles (emphasis added).

Further, at page 48, lines 4-7, the specification clearly describes the expression pattern of B305D as being "...highly over-expressed in breast tumors, prostate tumors, normal prostate tissue and testis compared to normal tissues, including normal breast tissue. Different splice variants of B305D have been identified with form A and C being the most abundant but all tested have similar tissue profiles in quantitative PCR."

In the same Example, at page 42, lines 3-7, the specification describes:

> The GABAπ mRNA levels were over-expressed in breast tumors. Previous studies had demonstrated its overexpression in uterus and to some degree in prostate and lung (Hedblom et al., J Biol. Chem. 272:15346-15350 (1997)) but no previous study had indicated elevated levels in breast tumors.

At page 48, lines 10-21, the specification further elaborates:

> This gene is a member of the $GABA_A$ receptor family and encodes a protein that has 30-40% amino acid homology with other family members, and has been shown by Northern blot analysis to be over-expressed in lung, thymus and prostate at low levels and highly over-expressed in uterus. Its expression in breast tissue has not been previously described. This is in contrast to other $GABA_A$ receptors that have appreciable expression in neuronal tissues. Tissue expression profiling of this gene showed it to be over-expressed in breast tumors in an inverse relationship to the B305D gene (Table 3). GABAπ detected 15/25 tumors and 6/21 metastases including 4 tumors and 5 metastases missed by mammaglobin. In contrast, B305D detected 13/25 breast tumors and 8/21 metastases, again including 3 tumors and 2 metastases missed by mammaglobin. A combination of just B305D and the GABAπ would be predicted to identify 22/25 breast tumors and 14/21 metastases (emphasis added).

Thus, the specification as filed clearly demonstrates that the recited sequences of SEQ ID NOs:7 and 75 are expressed at least two-fold higher in breast tumor tissue as compared to normal breast tissue and further, are not expressed in the majority of other normal tissues (in particular, normal resting and activated PBMC; see Figure 7). Also, the Examples of the specification as filed clearly demonstrate how to make and use the recited sequences in the detection of breast cancer cells either alone or in combination with other breast tumor markers. In particular, one diagnostic scenario where these sequences can be used and which is

exemplified in the specification as filed is in the identification of breast-derived cells in secondary locations. For example, in patients diagnosed with breast cancer, identification of breast-derived cells in blood would indicate metastasis, a key piece of information for proper treatment regimen. In such a scenario, expression in other tissues such as lung, thymus or prostate would not bar utility of identification of breast-derived cells in the blood since the patient is already diagnosed as having breast cancer and it would be highly unlikely that the cells would be derived from other tissues.

Concerning the allegation that in order to be useful for the diagnosis of breast cancer, it would need to be shown that either the sequences of SEQ ID NOs:7 and 75 are expressed only in cancer tissue to the exclusion of normal tissue or are expressed at a significantly higher level in cancer tissue (overexpressed) as compared to normal tissues, Applicants respectfully submit that, while these expression patterns are certainly ideal, they are by no means the only expression patterns that permit the diagnosis of cancer. For example, as would be readily appreciated by the skilled artisan, a sequence that is expressed in normal breast tissue and breast cancer tissue (that is, a sequence having a breast-specific expression pattern) can be used in the detection of metastatic breast cancer cells that have escaped the site of a primary breast tumor. In this diagnostic scenario, expression of the sequence in normal breast tissue is inconsequential. The effectiveness of tissue-specific, as opposed to tumor-specific, polynucleotides and polypeptides in the diagnosis of cancer, is further evidenced by the present widespread use of Prostate Specific Antigen (PSA), a prostate tissue-specific protein, to diagnose the presence of prostate cancer.

Mammaglobin is another well-known breast cancer marker that demonstrates a tissue-specific expression pattern. See U.S. Patent No. 5,668,267 (enclosed), issued based on the following data:

- Expression of mammaglobin was observed in normal breast tissue and breast cancer tissue, but not in a panel of other normal tissues. (See Figure 4B.)
- Higher mammaglobin expression was observed in only about 27% of breast cancer samples tested. (See Figure 4A and Column 6, line 62.)

The inventors conclude, "the expression of mammaglobin mRNA is relatively specific for mammary tissue" (see Column 13, lines 15-16). Utility for detecting breast cancer was established based on this data and claims to the isolated polynucleotide issued on September 16, 1997.

Additionally, mammaglobin has been shown to be an effective marker for detecting breast cancer cells in peripheral blood: see enclosed article by Zehentner, *et al.* 2004 Clinical Chemistry 50:11 2069-2076. Using techniques such as those described in the instant specification as filed (see e.g., the Examples), Zehentner, *et al.*, detect mammaglobin transcripts in circulating metastatic tumor cells in peripheral blood samples from breast cancer patients. Thus, Applicants submit that the gene expression patterns apparently required by the PTO are unduly restrictive and do not, in fact, reflect the current practice of cancer diagnostics.

Applicants submit that the claimed invention is enabled by the present disclosure. Reconsideration of the claims and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph are respectfully requested.

In view of the above remarks, the claims are now believed to be in condition for allowance. However, should any further issue require attention prior to allowance, the Examiner is requested to contact the undersigned at 206-622-4900 to resolve same.

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The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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JAU:ms

Enclosures:

Copy of US Patent No. 5,668,267
Copy of Zehentner, *et al.* 2004 Clinical Chemistry 50:11 2069-2076

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